UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/308,223	08/12/1999	GEORG KALLMEYER	P8341-9011	5876

6449 7590 11/29/2006

ROTHWELL, FIGG, ERNST & MANBECK, P.C.
1425 K STREET, N.W.
SUITE 800
WASHINGTON, DC 20005

EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 11/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/308,223
Filing Date: August 12, 1999
Appellant(s): KALLMEYER ET AL.

Monica Chin Kitts
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 8/16/2006 appealing from the Office action mailed 11/1/2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) **Evidence Relied Upon**

	Andya et al.	**4-1996**
6,267,958		
5,919,443	**Michaelis et al.**	**6-1995**

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 13, 15-18 and 22-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andya *et al.* (US Patent No. 6,267,958, March 1996) in view of Michaelis *et al.* (US Patent No. 5,919,443, June 1995).

Andya *et al.* teach a variety of lyophilizates comprising monoclonal or polyclonal antibodies, sugars, amino acids, and surfactants wherein the lyophilizate is essentially free of polyethylene glycols and additional proteins; wherein the lyophilizate contains a single amino acid or two different amino acids; wherein the lyophilizate further comprises a buffering agent or an isotonizing agent which is present in an amount such that a reconstituted solution of the lyophilizate has a pH value of 5-8 (columns 3-5); wherein the lyophilizate is storage-stable for a time period of at least three months at a temperature of about 4-12^{0}C (column 8, lines 45+, columns 3-5); wherein the sugar comprises at least one member selected from the group consisting of a monosaccharide, a disaccharide and a trisaccharide (column 15 line 12); wherein the sugar comprises sucrose or trehalose; wherein the amino acid comprises histidine, glutamic acid; wherein the surfactant comprises a polysorbate (column 15); wherein the monoclonal or the polyclonal antibody is directed against an antigen selected from the group consisting of integrins and or other antigens (column 7). Andya *et al.* further teach a variety of lyophilizates comprising monoclonal or polyclonal antibodies, sugars, amino acids, and surfactants, and an inorganic acid as a buffering agent (column 9, line 44); wherein the lyophilzate is dissolved in a physiologically acceptable solution; has a pH of 5-8; contains 1-10mg/ml of antibody (column 17). Andya *et al.* broadly anticipate a method of preparing a lyophilizate comprising mixing a buffered solution containing a monoclonal antibody or polyclonal antibody, a sugar, at least one amino acid and a surfactant, to prepare a mixed solution, wherein the mixed solution has a pH value of 5-8; and lyophilizing the mixed solution, wherein the lyophilizate is essentially free of polyethylene glycols and additional proteins. Further the molar concentrations of sugars, amino acids, and surfactants as claimed in claims 31-33 are also anticipated by Andya *et al.* (see columns 3-5).

Andya *et al.* do not include the teachings of an amino sugar such as glucosamine, N-methyl-glucosamine, galactosamine, and neuraminic acid.

Michaelis *et al.* teach the advantages of an improved lyophilizate which contains amino sugars (column 4,lines 1-6)

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the invention was made to modify the lyophilizate of Andya *et al.* so as to include an amino sugar as taught by Michaelis *et al.* One would have been motivated to do so because Michaelis *et al.* make the surprising discovery that it is possible to produce stable forms of pharmaceutical agents when maltose, raffinose, sucrose, trehalose or amino sugars are used as additives (column 3, line 9). Michaelis *et al.* further teach that solid preparations which contain maltose, raffinose, sucrose, trehalose or amino sugars as auxiliary agents can be frozen or even stored at increased temperatures with no significant loss of protein quality. Hence, the teachings of Michaelis *et al.* suggest an improved and more versatile lyophilizate which can also contain amino sugar.

(10) Response to Argument

Appellants respectfully point out that among proteins different stabilizers are required, not all stabilizers are suitable for all proteins. For example, Appellants submit that Osterberg (WO 94,07510, IDS) state on page 4, lines 25-32 that:

> "Proteins are different with regard to physio-chemical properties. When preparing a pharmaceutical preparation which should be physico-chemical acceptable, and stable for a long time, consideration cannot only be taken to the physiological properties of the protein but also other aspects must be considered such as industrial manufacture, easy handling for the patient and safety for the patient. **The results of these aspects are not predictable when testing different formulations and there often is a unique solution for each protein,**" (emphasis added).

As such, Appellants submit that Osterberg points out that different proteins are different in their physiochemical properties and thus for each protein or class of proteins an individual solution has to be developed and thus, it cannot be predicted that the same formulation will be useful for a different class of proteins. Moreover, Appellants submit that Manning (Pharmaceutical Research, Vol. 6., No. 11, 1989, p. 903-918) states on page 913, left column, first sentence of the last paragraph, that "protein stability encompasses many complicated and interrelated chemical and physical process". From this, Appellants contend that for every protein or class of proteins an individual solution has to be found due to different physical and chemical constraints. Furthermore, Appellants submit that Osterberg's and Manning's conclusions are supported by the fact that

different substances are indicated as good stabilizers in some references and as not useful stabilizers in other references. For example, Appellants submit that Kunihiro (EP 0 689 843) page 4, line 4 - 7, indicates that the combination of soluble thrombomodulin together with albumin, purified gelatin, glycine, glucose or mannitol **failed** to exhibit sufficient long term stability. Thus Appellants argue that this document contradicts the contention in the office action that Michaelis' teaching can be applied to any and all pharmaceutical preparations because Kunihiro teaches away from the current invention in that the combination of an amino acid with a sugar had no beneficial effect on stability. Appellants further point to Hanson (chapter 7 in Stability of Protein Pharmaceuticals, 1992) whom indicates on page 217, second paragraph, line 6 to 7 that "Ornithine, aspartic acid, glutamic acid, alanine and glycine did not stabilize" intravenous immunoglobulin preparations. Thus, Appellants contend that Hanson also contradicts the contention in the office action that Michaelis' teaching can be applied to any and all pharmaceutical preparations and teaches away from the current invention which shows that the use of the amino acids listed in Hanson improve the stability of the lyophilized antibody formulation. In addition, Appellants argue that Metzner (EP 0 733 702) which is equivalent to US Patent No. 6,204,036 indicates that histidine and glutamic acid alone, even without further additives, show sufficient stabilization (page 3, line 9, of the German text, column 5, lines 56-58 of the US text). In contrast to Metzner, Appellants submit that Michaelis (WO 94/14465) states on page 10, lines 4 to 7 of the German WO 94/14465 that the addition of glutamic acid has no significant impact on the storage stability. Moreover, Appellants submit that both Metzner and Michaelis indicate that the surfactant had no impact on storage stability (Metzner page 3, lines 42-43 or col. 6, lines 48-50 in the U.S. Patent, Michaelis page 9, last paragraph of WO 94/14465) but the present inventors have found that the surfactant does affect stability in the present invention. Thus, Appellants argue that formulations for stabilizing different pharmaceutical preparations clearly cannot be generalized. Moreover, Appellants assert that Nema (J. Parent Sci. Technol., 47, p. 76-83, 1993) states on page 81, left column, last sentence of the first paragraph: "A surprising result was obtained with trehalose, a disaccharide which is considered by many workers to be one of the best cryoprotectants, but proved to be ineffective in this study at a concentration of 5% W/V". In view of this, Appellants contend that this statement also supports the conclusion of the non-transferability of formulations to different classes of protein. Appellants further point out that three things can be concluded from the above references:

1) Though there are diverse citations showing that the use of a single compound can improve the stability of formulations markedly, there is no suggestion that a combination of different compounds discussed in different references will result in a formulation with further improved stability. Furthermore, there is no hint in these documents as to the particular combination of compounds as described in the current invention.

2) As can be seen from these references, it is not possible to transfer the composition of a formulation useful with one class of proteins or with one protein to other proteins. It is not probable or even predictable that such a transfer might be successful.

3) There are no cited documents that suggest or disclose that a formulation for stabilizing a non-antibody protein can be used for the stabilization of a lyophilized antibody preparation.

Appellants also point out that Michaelis shows amino sugar containing preparations in Example 5. From table 6 and 7, Appellants submit that it can be seen that a combination containing G-CSF plus a surfactant plus an amino sugar plus one amino acid has poor stability compared to formulations containing an amino sugar, a second non- amino sugar and optionally an amino acid. Thus, Appellants argue that Michaelis does not suggest the combination as claimed by the current application which uses an amino sugar, at least one amino acid and a surfactant to stabilize antibodies. Thus, Appellants contend that even if one skilled in the art were to combine Michaelis with Andya (which as discussed above, they would not) they would not arrive at the present invention. Appellants contend that one skilled in the art would not expect Michaelis' formulation to be useful for any and all pharmaceutical preparations as different proteins require different stabilization agents and there is no reason to believe that Michaelis' formulation would stabilize antibody preparations. In addition, Appellants point out that Michaelis found that a preparation similar to the present invention (which uses an amino sugar, at least one amino acid and a surfactant) resulted in less stability for G-CSF.

These arguments have been carefully considered, but are not found persuasive.

Regarding the references cited by Appellants to argue that there is no suggestion that a combination of different compounds discussed in different references will result in a formulation with further improved stability, the Examiner acknowledges and agrees with Appellants contention that there is no suggestion that **a combination of different compounds discussed in different references** will result in a formulation with further improved stability (emphasis added). However,

the Examiner recognizes that the fact patterns involved in the instant situation are different from those discussed and argued by Appellants. In the instant case, Andya, a single reference, teach a lyophilizate comprising monoclonal or polyclonal antibodies, sugars, amino acids, and surfactants wherein the lyophilizate is essentially free of polyethylene glycols and additional proteins, where as Michaelis et al., a single reference, teach the advantages of an improved lyophilizate which contains amino sugars. Thus, in agreement with Appellants statement that there are diverse citations showing that the use of a single compound can improve the stability of formulations markedly, Michaelis et al. suggests, *supra*, the motivation to combine a singe compound such as an amino sugar in the formulation taught by Andya. Moreover, it must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which make up the state of the art with regard to the claimed invention. Furthermore, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In the instant case, both references represent analogous teachings comprising the preparation of stable pharmaceutical compositions. In response to Appellants contention that the combination of Michaelis (Example 5, Table 6 and 7) containing G-CSF plus a surfactant plus an amino sugar plus one amino acid has poor stability compared to formulations containing an amino sugar, a second non- amino sugar and optionally an amino acid, the Examiner acknowledges Appellants interpretation of the results shown in Table 6 and 7 of Example 5. However, the Examiner recognizes that Michaelis appears to teach the opposite. For example, the % DCP (decomposition product) for Formulation 11, which contains an amino sugar (N-methyl glucosamine), an amino acid (phenylalanine) and a surfactant (maltrose) was 1.2 and 1.8 at 8°C and 40°C respectively, where as the %DCP for Formulation 14 containing an amino sugar (N-methyl-glucosamine), glycine (amino acid) and a non-amino acid (Plunaria) was 1.2 and 3.5 at 8°C and 40°C respectively. As such, it appears the Formulation 11 is more stable than the Formulation of 14. Therefore, Appellant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Brandon Fetterolf, PhD

Brandon Fetterolf, PhD

Conferees:

Jeff Siew

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER

Gary Nickol, PhD.

Gary B Nickol

GARY B. NICKOL, PH.D.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600